UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,354	08/10/1999	STEPHEN DONOVAN	17310	9137

7590 10/18/2002

STEPHEN DONOVAN
LEGAL DEPTALLERGAN INC TOWER TWO 7TH FLR
2525 DUPONT DRIVE
IRVINE, CA 926239534

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/18/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/371,354	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communicati n appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,15-17,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,15-17,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 29 April 2002 (Paper No. 12) under 37 CFR 1.114 based on parent Application No. 09/371,354 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application and/or Claims

The amendment of 24 July 2002 (Paper No. 17) has been entered. Claims 7, 15-17, and 38 are amended and claims 9-10, 12-13, and 35-36 are cancelled. Page one of the specification was not replaced because replacement pages are not entered under 37 CFR 1.121.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7, 15-17, and 37-38 are under consideration in the instant application.

Information Disclosure Statement

1. The references listed on the current and previous PTO-1449 forms (29 April 2002, Paper No. 14; 05 December 2001, Paper No. 8) have already been considered by the Examiner. These references were included with the PTO-1449 forms of 19 August 1999, 19 October 1999, and 02 January 2001 (Paper Nos. 1-3). The references are crossed out on the current and previous PTO-1449 so as to prevent duplication at the printers if the application ever issues as a patent.

Claim Rejections - 35 USC § 112

2. Claims 7, 15-17, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7, 15-17, and 37-38 are directed to a method for treating bradycardia comprising intrapericardial injection of a botulinum toxin to an SA node or to an AV node of a heart of a patient with bradycardia to treat bradycardia. The claims also recite that botulinum toxin is botulinum toxin A and is locally administered to the heart in an amount between 0.01 U/kg and 35 U/kg, between 0.1 U/kg and 30 U/kg, between 1U/kg and 25 U/kg. The basis for this rejection is set forth at pg 3-8 of the previous Office Action (Paper No. 11, 25 February 2002) and the Office Action of 05 July 2001 (Paper No. 6).

Applicant's arguments (Paper No. 17, 24 July 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the November 5, 2001 declaration from Dr. John Longhurst establishes Dr. Longhurst as an expert in the field of cardiovascular medicine and specifically in the treatment of cardiac disorders, such as bradycardia (pg 6 of Applicant's Response of 24 July 2002). Applicant argues that when the declarant states that he has read the present application and gives his expert opinion, it would appear to be obvious that the declarant has done so by drawing upon his vast and extensive training and experience as a scientist and physician to reach a reasoned scientific conclusion (pg 7 of Response). Applicant contends that according to the declarant's opinion, a cardiologist of ordinary skill in the art can successfully practice the claimed invention. Applicant also indicates that the declarant has supported his opinion with scientific reasoning (pg 9 of Response). At page 12-13 of the Response, Applicant argues that the present invention is not unpredictable and complex, due to the submitted declarations.

Applicant's arguments have been fully considered but are not found to be persuasive. The declaration under 37 CFR 1.132 filed 29 April 2002 (Paper No. 13) is insufficient to overcome the rejection of claims 7, 15-17, and 37-38 based upon lack of enablement under 35 U.S.C. § 112, first paragraph as set forth in the previous Office actions. Although Dr. Longhurst has extensive training and experience as a scientist and physician in cardiovascular medicine, Dr. Longhurst has not worked with any botulinum toxins. Additionally, Dr. Longhurst has not investigated what effects local administration of botulinum toxin has upon any internal body organ, particularly the heart. Although paragraph 2 of the declaration may be well known facts, the skilled artisan cannot predict that intrapericardial injection of any botulinum toxin into the SA or AV node of the heart of patient will produce the desired response, i.e. an increased heart rate, because the heart is a complex organ and numerous challenges of botulinum therapy have been reported (Johnson, E. Ann Rev Microbiol 53: 551-575, 1999; pg 566).

(ii) Applicant states that the five "complications" of botulinum toxin therapy discussed in the previous Office Action were also taken from pg 566 of Johnson, E.A. (Ann Rev Microbiol 53: 551-575, 1999). Applicant argues that the Johnson article was published in a microbiology journal, not in a medical journal. Applicant also makes the point that Eric Johnson is a microbiologist, not a physician. Applicant concludes that since Eric Johnson is not a physician, he has not and cannot treat patients with any affliction for any purpose (pg 11 of Response). Applicant again indicates that botulinum toxin has been used therapeutically in clinical settings since 1978 to treat many target tissues. Applicant notes that in 1989 the FDA approved botulinum toxin type A for the treatment of blepharospasm and strabismus. Applicant also states

that in 2000, the FDA approved botulinum toxins types A and B for the treatment of cervical dystonia and in 2002, the FDA approved botulinum toxin A to treat certain facial wrinkles. Applicant asserts that physicians have extensive experience with the use of botulinum toxins and the FDA has approved several botulinum toxins to treat various afflictions (pg 11-12 and 16-17 of Response). Applicant also argues with regard to the five complications of botulinum toxin therapy: (1) if antibodies develop to a type A toxin at least one alternate and FDA approved serotype is available; (2) there is not a lack of alternate botulinum serotypes to use; (3) the issue of the toxin diffusing to neighboring muscles is addressed by practitioners adjusting the amount of toxin used; (4) the lack of consistency and low specific activities is non-existent in light of the FDA approvals; (5) many, if not all, pharmaceuticals require at least some repeat dosing to treat a chronic condition.

Applicant's arguments have been fully considered but are not found to be persuasive. The Johnson reference cited by the Examiner was utilized to indicate the state of the art at the time the invention was made. In particular, the Johnson reference discusses the challenges of botulinum toxin A therapy and the unpredictability of the effects of botulinum toxin in a subject. Such complications include "(a) formation of antibodies and obliteration of response to type-A toxin, (b) lack of alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating ptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for repeated injection of toxin in chronic disorders" (Johnson, pg 566, pp 1). Applicant attempts to explain that the five complications put forth by Johnson can be overcome. Applicant contends that at least one alternate toxin serotype is available if

antibodies form against botulinum toxin A. However, alternate serotypes may elicit antibody formation or may not have the same potency of action to treat the condition. Although Applicant states that there is not a lack of alternate botulinum serotypes to use, there are only serotypes A-G. Serotypes other than A do not have the potency and duration of action of botulinum type A. Applicant cites Berardellu et al. (Mov Disord 17(Supp 2): s70-s74, 2002) to emphasize that adjusting the amount of toxin will address the issue of toxin diffusing to neighboring muscles. However, this reference discusses cranial dystonia and not bradycardia. The paragraph at pg S73 of the article also does not discuss how an optimal dose is chosen to prevent diffusion to neighboring muscles. Applicant argues that the lack and low specific activities of certain toxin preparations is non-existent because the FDA has approved several toxin serotypes. However, the FDA has only approved botulinum toxin A for the treatment of blepharospasm and strabismus, botulinum toxins A and B for the treatment of cervical dystonia, and botulinum toxin A for certain facial wrinkles. Therefore, there still remains a lack of consistency and low specific activities of certain toxin preparations. Furthermore, regarding the problem that there is a need for repeated injection of toxin in chronic disorders, Applicant asserts that many pharmaceuticals require at least some dose repeat. However, in reference to the instant application, administration of botulinum toxin to the heart would be complex and the effects of repeated administration is unknown.

It is also noted that although Eric Johnson is not a physician, he is qualified to write such an article because he is a microbiologist that studies *Clostridium botulinum* and its toxins.

The Examiner acknowledges that the FDA has approved botulinum toxin A for the treatment of blepharospasm and strabismus, botulinum toxins A and B for the treatment of

cervical dystonia, and botulinum toxin A for certain facial wrinkles. However, these FDA approvals do not change the fact that a large quantity of experimentation is necessary to determine the dosage and safety of botulinum toxin when administered to the heart, as well as the timing and duration of treatment. The FDA approvals also do not predict the effects of botulinum toxin when administered to the heart. If anything, the FDA approvals indicate that rigorous background research and experiments (and eventually clinical trials) must be performed in order for each type of botulinum toxin therapy to be considered safe and effective for patients. There are no methods or working examples in the instant specification to indicate that intrapericardial injection of a botulinum toxin to an SA node or to an AV node of a heart of a patient with bradycardia will treat the bradycardia.

(iii) Applicant contends at page 13-16 of the Response that it is not a requirement to provide working examples in the application. Applicant asserts that it is well established case law that a specification need not contain working examples if, coupled with information known in the art, the invention is otherwise disclosed in the specification in such a manner that one skilled in the art will be able to practice it without undue experimentation (*in re Borkowski and Van Venrooy*, 164 USPQ 642 (CCPA 1970)). Applicant submits that detailed methods for intrapericardial administration of a botulinum toxin to treat bradycardia have been disclosed. Applicant also argues that the specification discloses how to inject the toxin, where to inject the toxin, appropriate formulations of the toxin, and the range of the toxin dose to use.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification at pg 31-33 outlines a prophetic procedure for treating bradycardia by

administering botulinum toxin A to an SA node to an AV node of a heart of a patient. However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. For example, the prophetic example does not teach the skilled artisan the *optimal* dosage and duration of administration of botulinum toxin A. The specification only teaches that "the specific unit amount of BOTOX to locally administer depends upon a number of factors,...including the age and health of the patient, the size of the patient's heart, the mass of the arrhythmic cardiac tissue of the patient's heart, the local administration route and mechanism chosen, etc." (pg 33, lines 10-14). Furthermore, the claimed method may not necessarily treat bradycardia. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage and duration of administration of botulinum toxin A. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as discussed in the previous Office Action, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat bradycardia by intrapericardial injection of a botulinum toxin to an SA node or AV node of a heart of a patient. Although the

claimed method utilizes routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin. There is no information in the art regarding injection of botulinum toxins into major organs of the body and the invention of the instant application is not disclosed in the specification in such a manner that one skilled in the art will be able to practice it without undue experimentation.

(iv) Applicant argues at pages 14-15 and 17-20 of the Response that there is guidance in the specification as to the safe dosage and duration of administration of any botulinum toxin to the heart muscle. Applicant also states that a cardiologist of ordinary skill knows how to access the pericardial space of a patient with bradycardia and knows how to inject a pharmaceutical such as botulinum toxin into the pericardial space.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above, the specification only teaches that "the specific unit amount of BOTOX to locally administer depends upon a number of factors,...including the age and health of the patient, the size of the patient's heart, the mass of the arrhythmic cardiac tissue of the patient's heart, the local administration route and mechanism chosen, etc." (pg 33, lines 10-14). However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The specification of the instant application does not teach the skilled artisan a specific safe dosage or duration of treatment of any botulinum toxin to the heart muscle. Undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered to every patient without damage to the heart. Furthermore, although a cardiologist knows how to access

the pericardial space of a patient with bradycardia and knows how to inject a pharmaceutical into the pericardial space, this does not mean that a cardiologist or other such skilled artisan can *treat* bradycardia by injecting a botulinum toxin to an SA or AV node of a heart of a patient with bradycardia.

(v) Regarding the Examiner's assertion of contradictory state of the prior art, Applicant contends at pg 21 of the Response that Lamanna (Arch Int Pharmacodyn 293: 69-83, 1988) does not disclose or suggest intrapericardial (local) administration of a botulinum toxin. Applicant indicates that Lamanna discloses administration of a botulinum toxin systemically by intravenous injection and administration of a botulinum toxin to an isolated heart. Applicant argues that Lamanna concludes that the toxin administered acts upon the heart through a physical, as opposed to a chemical (cell receptor) mechanism. Applicant emphasizes that Lamanna states "Our findings...rule against the vagal nerve-SA junction as a primary site of action for the heart changes observed in our study". Applicant asserts at pg 22-23 of the Response that Lamanna is not contradictory art with regard to the present invention because the observations of Lamanna result from different experimental protocol. Applicant states that Lamanna uses systemic or isolated heart toxin application, while the instant application utilizes intrapericardial administration to the SA or AV nodes of the heart.

Applicant's arguments have been fully considered but are not found to be persuasive. The Lamanna reference cited by the examiner in the previous Office Actions is to establish the state of the art at the time the invention was disclosed. Lamanna discusses the challenges of botulinum toxin therapy, such as temporary bradycardia and electrocardiographic (ECG) changes

(pg 69-70, abstract). Although the complications observed by Lamanna arise after intravenous injection of botulinum toxin and administration of botulinum toxin to an isolated heart, similar problems may be possibly observed after the intrapericardial injection of botulinum toxin to the SA node or AV node of the heart as claimed in the instant application. However, there are no methods or working examples to indicate that the claimed method is free of the complications experienced by Lamanna. There are also no methods or working examples in the specification to indicate that intrapericardial administration of any botulinum toxin into the SA node or AV node inhibits parasympathetic (cholinergic/vagal) nerve activity of a bradycardiac heart, resulting in uninhibited sympathetic innervation to increase heart rate. Also, even if Lamanna concludes from their findings that the botulinum toxin administered acts upon the heart through a physical, as opposed to a chemical (cell receptor) mechanism, a compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the dosage and safety of botulinum toxin and the timing and duration of administration, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Johnson and Lamanna et al.), the unpredictability of the effects any botulinum toxin on a subject (see discussion and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 7, 15-17, and 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Regarding claims 7, 15-17, and 37-38, the acronyms "SA node" and "AV node" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

5. Claims 7, 15-17, and 37-38 are rejected as being indefinite for the recitation of "an SA node" and "an AV node". It is not clear what other SA nodes and AV nodes Applicant is referring to. There is only one SA node and one AV node in the heart. (Please note this issue could be overcome by replacing the term "an" with "the".)

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
October 16, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER